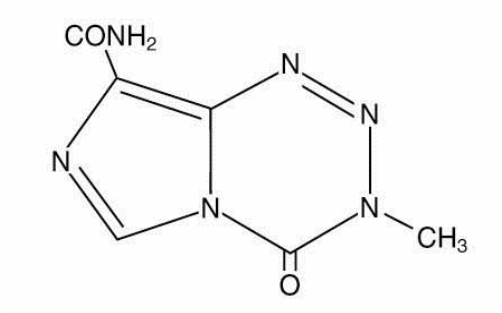
F-XXXXXXXX

PRODUCT INFORMATION

TEMODAR® (temozolomide) CAPSULES

DESCRIPTION

TEMODAR Capsules for oral administration contain temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-*a*s-tetrazine-8-carboxamide. The structural formula is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence TEMODAR can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Each capsule contains either 5 mg, 20 mg, 100 mg, or 250 mg of temozolomide. The inactive ingredients for TEMODAR Capsules are lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. Gelatin capsule shells contain titanium dioxide. The capsules are white and imprinted with pharmaceutical ink.

TEMODAR 5 mg: green imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, titanium dioxide, yellow iron oxide, and FD&C Blue #2 aluminum lake.

TEMODAR 20 mg: brown imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, titanium dioxide, black iron oxide, yellow iron oxide, brown iron oxide, and red iron oxide.

TEMODAR 100 mg: blue imprint contains pharmaceutical glaze (modified) in an ethanol/shellac mixture, isopropyl alcohol, n-butyl alcohol, propylene glycol, titanium dioxide, and FD&C Blue #2 aluminum lake.

TEMODAR 250 mg: black imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, and black iron oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.

Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and T_{max} increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast. Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC) which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m^2.

Special Populations: *Age* Population pharmacokinetic analysis indicates that age (range 19 to 78 years) has no influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age (see **PRECAUTIONS**).

Gender Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men (see **ADVERSE REACTIONS**).

Race The effect of race on the pharmacokinetics of temozolomide has not been studied.

Tobacco Use Population pharmacokinetic analysis indicates that the oral clearance of temozolomide is similar in smokers and nonsmokers.

Creatinine Clearance Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m^2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr <36 mL/min/m^2). Caution should be exercised when TEMODAR Capsules are administered to patients with severe renal impairment. TEMODAR has not been studied in patients on dialysis.

Hepatically Impaired Patients In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild-to-moderate hepatic impairment (Child's-Pugh Class I - II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

Drug-Drug Interactions In a multiple-dose study, administration of TEMODAR Capsules with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC. Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5% (see **PRECAUTIONS**).
Population analysis failed to demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

CLINICAL STUDIES

Newly Diagnosed Glioblastoma Multiforme Five hundred and seventy-three patients were randomized to receive either TEMODAR (TMZ) + Radiotherapy (RT) (n= 287) or RT alone (n=286). Patients in the TEMODAR + RT arm received concomitant TEMODAR (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by 6 cycles of TEMODAR alone (150 or 200 mg/m^2) on Day 1-5 of every 28-day cycle, starting 4 weeks after the end of RT. Patients in the control arm received RT only. In both arms, focal radiation therapy was delivered as 60 Gy/30 fractions. Focal RT includes the tumor bed or resection site with a 2-3 cm margin. *Pneumocystis carinii* pneumonia (PCP) prophylaxis was required during the TMZ + radiotherapy treatment, regardless of lymphocyte count, and was to continue until recovery of lymphocyte count to less than or equal to Grade 1.

At the time of disease progression, TEMODAR was administered as salvage therapy in 161 patients of the 282 (57%) in the RT alone arm, and 62 patients of the 277 (22%) in the TEMODAR + RT arm.

The addition of concomitant and maintenance TEMODAR to radiotherapy in the treatment of patients with newly diagnosed GBM showed a statistically significant improvement in overall survival compared to radiotherapy alone (Figure 1). The hazard ratio (HR) for overall survival was 0.63 (95% CI for HR=0.52-0.75) with a log-rank p <0.0001 in favor of the TEMODAR arm. The median survival was increased by 2 ½ months in the TEMODAR arm.

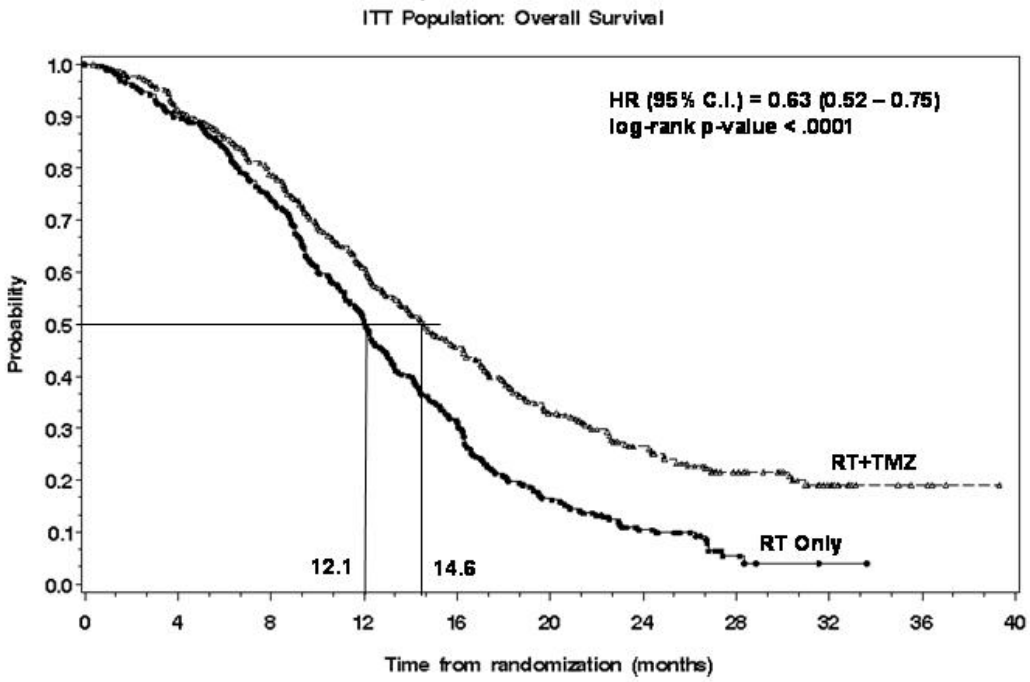


Figure 1 Kaplan-Meier Curves for Overall Survival (ITT Population)

Refractory (Anaplastic Astrocytoma)

A single-arm, multicenter study was conducted in 162 patients who had anaplastic astrocytoma at first relapse and who had a baseline Karnofsky performance status of 70 or greater. Patients had previously received radiation therapy and may also have previously received a nitrosourea with or without other chemotherapy. Fifty-four patients had disease progression on prior therapy with both a nitrosourea and procarbazine and their malignancy was considered refractory to chemotherapy (refractory anaplastic astrocytoma population). Median age of this subgroup of 54 patients was 42 years (19 to 76). Sixty-five percent were male. Seventy-two percent of patients had a KPS of >80. Sixty-three percent of patients had surgery other than a biopsy at the time of initial diagnosis. Of those patients undergoing resection, 73%

underwent a subtotal resection and 27% underwent a gross total resection. Eighteen percent of patients had surgery at the time of first relapse. The median time from initial diagnosis to first relapse was 13.8 months (4.2 to 75.4).

TEMODAR Capsules were given for the first 5 consecutive days of a 28-day cycle at a starting dose of 150 mg/m^2/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count was >1.5 x 10^9/L (1,500/µL) and the nadir and Day 29, Day 1 of next cycle, platelet count was >100 x 10^9/L (100,000/µL), the TEMODAR dose was increased to 200 mg/m^2/day for the first 5 consecutive days of a 28-day cycle.

In the refractory anaplastic astrocytoma population, the overall tumor response rate (CR + PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54 patients). The median duration of all responses was 50 weeks (range of 16 to 114 weeks) and the median duration of complete responses was 64 weeks (range of 52 to 114 weeks). In this population, progression-free survival at 6 months was 45% (95% confidence interval 31% to 58%) and progression-free survival at 12 months was 29% (95% confidence interval 16% to 42%). Median progression-free survival was 4.4 months. Overall survival at 6 months was 74% (95% confidence interval 62% to 86%) and 12-month overall survival was 65% (95% confidence interval 52% to 78%). Median overall survival was 15.9 months.

INDICATIONS AND USAGE

TEMODAR (temozolomide) Capsules are indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

TEMODAR Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

CONTRAINDICATIONS

TEMODAR (temozolomide) Capsules are contraindicated in patients who have a history of hypersensitivity reaction to any of its components. TEMODAR is also contraindicated in patients who have a history of hypersensitivity to DTIC, since both drugs are metabolized to MTIC.

WARNINGS

Patients treated with TEMODAR Capsules may experience myelosuppression. Prior to dosing, patients must have an absolute neutrophil count (ANC) $\geq$1.5 x 10^9/L and a platelet count $\geq$100 x 10^9/L. A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L and platelet count exceeds 100 x 10^9/L.Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression. Very rare cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have also been observed.

For treatment of newly diagnosed glioblastoma multiforme: Prophylaxis against *Pneumocystis carinii* pneumonia is required for all patients receiving concomitant TEMODAR and radiotherapy for the 42 day regimen.

There may be a higher occurrence of PCP when temozolomide is administered during a longer dosing regimen. However, all patients receiving temozolomide, particularly patients receiving steroids, should be observed closely for the development of PCP regardless of the regimen.

Pregnancy: Temozolomide may cause fetal harm when administered to a pregnant woman. Five consecutive days of oral administration of 75 mg/m^2/day in rats and 150 mg/m^2/day in rabbits during the period of organogenesis (3/8 and 3/4 the maximum recommended human dose, respectively) caused numerous malformations of the external organs, soft tissues, and skeleton in both species. Doses of 150 mg/m^2/day in rats and rabbits also caused embryolethality as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMODAR Capsules.

PRECAUTIONS

Information for Patients: Nausea and vomiting were among the most frequently occurring adverse events. These were usually either self-limiting or readily controlled with standard antiemetic therapy. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. The medication should be kept away from children and pets.

Drug Interaction: Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

Patients with Severe Hepatic or Renal Impairment: Caution should be exercised when TEMODAR Capsules are administered to patients with severe hepatic or renal impairment (see **Special Populations**).

Geriatrics: Clinical studies of temozolomide did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should be exercised when treating elderly patients.

In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia (2/8; 25%, p=0.31 and 2/10; 20%, p=0.09, respectively) in the first cycle of therapy than patients under 70 years of age (see **ADVERSE REACTIONS**).

In newly diagnosed patients with glioblastoma multiforme, the adverse event profile was similar in younger patients (<65 years) vs older (≥65 years).

Laboratory Tests: For the concomitant treatment phase with RT, a complete blood count should be obtained weekly.
For the 28 day treatment cycles**,** a complete blood count should be obtained on Day 22 (21 days after the first dose). Blood counts should be performed weekly until recovery if the ANC falls below 1.5 x 10^9/L and the platelet count falls below 100 x 10^9/L.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Standard carcinogenicity studies were not conducted with temozolomide. In rats treated with 200 mg/m^2 temozolomide (equivalent to the maximum recommended daily human dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were found in both males and females. With 6 cycles of treatment at 25, 50, and 125 mg/m^2 (about 1/8 to 1/2 the maximum recommended daily human dose), mammary carcinomas were observed at all doses and fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate; carcinoma of the seminal vesicles, schwannoma of the heart, optic nerve, and harderian gland; and adenomas of the skin, lung, pituitary, and thyroid were observed at the high dose.
Temozolomide was mutagenic *in vitro* in bacteria (Ames assay) and clastogenic in mammalian cells (human peripheral blood lymphocyte assays).
Reproductive function studies have not been conducted with temozolomide. However, multicycle toxicology studies in rats and dogs have demonstrated testicular toxicity (syncytial cells/immature sperm, testicular atrophy) at doses of 50 mg/m^2 in rats and 125 mg/m^2 in dogs (1/4 and 5/8, respectively, of the maximum recommended human dose on a body surface area basis).

Pregnancy Category D: See **WARNINGS** section.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TEMODAR Capsules, patients receiving TEMODAR should discontinue nursing.

Pediatric Use: TEMODAR effectiveness in children has not been demonstrated. TEMODAR Capsules have been studied in 2 open label Phase 2 studies in pediatric patients (age 3-18 years) at a dose of 160-200 mg/m^2 daily for 5 days every 28 days. In one trial conducted by the Schering Corporation, 29 patients with recurrent brain stem glioma and 34 patients with recurrent high grade astrocytoma were enrolled. All patients had failed surgery and radiation therapy, while 31% also failed chemotherapy. In a second Phase 2 open label study conducted by the Children's Oncology Group (COG), 122 patients were enrolled, including medulloblastoma/PNET(29), high grade astrocytoma (23), low grade astrocytoma (22), brain stem glioma (16), ependymoma (14), other CNS tumors (9), and non-CNS tumors (9). The TEMODAR toxicity profile in children is similar to adults. Table 1 shows the adverse events in 122 children in the COG Phase 2 study.

Table 1

Adverse Events Reported in Pediatric Cooperative Group Trial (≥10%)		
	No. (%) of TEMODAR Patients (N=122)[a]	
Body System/Organ Class Adverse Event	**All Events**	**Gr 3/4**
Subjects Reporting an AE	**107 (88)**	**69 (57)**
Body as a Whole		
Central and Peripheral Nervous System		
Central cerebral CNS cortex	22 (18)	13 (11)
Gastrointestinal System		
Nausea	56 (46)	5 (4)
Vomiting	62 (51)	4 (3)
Platelet, Bleeding and Clotting		
Thrombocytopenia	71 (58)	31 (25)
Red Blood Cell Disorders		
Decreased Hemoglobin	62 (51)	7 (6)
White Cell and RES Disorders		
Decreased WBC	71 (58)	21 (17)
Lymphopenia	73 (60)	48 (39)
Neutropenia	62 (51)	24 (20)

a: These various tumors included the following: PNET-medulloblastoma, glioblastoma, low grade astrocytoma, brain stem tumor, ependymoma, mixed glioma, oligodendroglioma, neuroblastoma, Ewing's sarcoma, pineoblastoma, alveolar soft part sarcoma, neurofibrosarcoma, optic glioma, and osteosarcoma.

ADVERSE REACTIONS IN ADULTS

Newly Diagnosed Glioblastoma Multiforme

During the concomitant phase (Temodar + radiotherapy), adverse events including thrombocytopenia, nausea, vomiting, anorexia, and constipation, were more frequent in the TEMODAR + RT arm. The incidence of other adverse events was comparable in the two arms. The most common adverse events across the cumulative TEMODAR experience were alopecia, nausea, vomiting, anorexia, headache, and constipation (see **Table 2**). Forty-nine percent (49%) of patients treated with TEMODAR reported one or more severe or life-threatening events, most commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia (5%). Overall, the pattern of events during the maintenance phase was consistent with the known safety profile of TEMODAR.

306 **Table 2 Number (%) of Patients with Adverse Events: All and Severe/Life**
307 **Threatening (Incidence of 5% or Greater)**
308

	Concomitant Phase RT Alone (n=285)		Concomitant Phase RT+TMZ (n=288)*		Maintenance Phase TMZ (n=224)	
	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3
Subjects Reporting any Adverse Event	**258 (91)**	**74 (26)**	**266 (92)**	**80 (28)**	**206 (92)**	**82 (37)**
Body as a Whole - General Disorders						
Anorexia	25 (9)	1 (<1)	56 (19)	2 (1)	61 (27)	3 (1)
Dizziness	10 (4)	0	12 (4)	2 (1)	12 (5)	0
Fatigue	139 (49)	15 (5)	156 (54)	19 (7)	137 (61)	20 (9)
Headache	49 (17)	11 (4)	56 (19)	5 (2)	51 (23)	9 (4)
Weakness	9 (3)	3 (1)	10 (3)	5 (2)	16 (7)	4 (2)
Central and Peripheral Nervous System Disorders						
Confusion	12 (4)	6 (2)	11 (4)	4 (1)	12 (5)	4 (2)
Convulsions	20 (7)	9 (3)	17 (6)	10 (3)	25 (11)	7 (3)
Memory Impairment	12 (4)	1 (<1)	8 (3)	1 (<1)	16 (7)	2 (1)
Disorders of the Eye						
Vision Blurred	25 (9)	4 (1)	26 (9)	2 (1)	17 (8)	0
Disorders of the Immune System						
Allergic Reaction	7 (2)	1 (<1)	13 (5)	0	6 (3)	0
Gastro-Intestinal System Disorders						
Abdominal Pain	2 (1)	0	7 (2)	1 (<1)	11 (5)	1 (<1)
Constipation	18 (6)	0	53 (18)	3 (1)	49 (22)	0
Diarrhea	9 (3)	0	18 (6)	0	23 (10)	2 (1)
Nausea	45 (16)	1 (<1)	105 (36)	2 (1)	110 (49)	3 (1)
Stomatitis	14 (5)	1 (<1)	19 (7)	0	20 (9)	3 (1)
Vomiting	16 (6)	1 (<1)	57 (20)	1 (<1)	66 (29)	4 (2)
Injury and Poisoning						
Radiation Injury NOS	11 (4)	1 (<1)	20 (7)	0	5 (2)	0
Musculo-Skeletal System Disorders						
Arthralgia	2 (1)	0	7 (2)	1 (<1)	14 (6)	0
Platelet, Bleeding and Clotting Disorders						
Thrombocytopenia	3 (1)	0	11 (4)	8 (3)	19 (8)	8 (4)
Psychiatric Disorders						
Insomnia	9 (3)	1 (<1)	14 (5)	0	9 (4)	0
Respiratory System Disorders						
Coughing	3 (1)	0	15 (5)	2 (1)	19 (8)	1 (<1)
Dyspnea	9 (3)	4 (1)	11 (4)	5 (2)	12 (5)	1 (<1)

	Concomitant Phase RT Alone (n=285)		Concomitant Phase RT+TMZ (n=288)*		Maintenance Phase TMZ (n=224)	
	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3
Skin and Subcutaneous Tissue Disorders						
Alopecia	179 (63)	0	199 (69)	0	124 (55)	0
Dry Skin	6 (2)	0	7 (2)	0	11 (5)	1 (<1)
Erythema	15 (5)	0	14 (5)	0	2 (1)	0
Pruritus	4 (1)	0	11 (4)	0	11 (5)	0
Rash	42 (15)	0	56 (19)	3 (1)	29 (13)	3 (1)
Special Senses Other, Disorders						
Taste Perversion	6 (2)	0	18 (6)	0	11 (5)	0

*One patient who was randomized to RT only arm received RT + temozolomide

RT+TMZ=radiotherapy plus temozolomide; LT=life threatening; SGPT = serum glutamic pyruvic transaminase (=alanine aminotransferase [ALT]); NOS=not otherwise specified.

Note: Grade 5 (fatal) adverse events are included in the Grade ≥ 3 column.

Myelosuppression, (neutropenia and thrombocytopenia), which are known dose limiting toxicities for most cytotoxic agents, including TEMODAR, were observed. When laboratory abnormalities and adverse events were combined, Grade 3 or Grade 4 neutrophil abnormalities including neutropenic events were observed in 8% of the patients and Grade 3 or Grade 4 platelet abnormalities, including thrombocytopenic events were observed in 14% of the patients treated with TEMODAR.

Refractory Anaplastic Astrocytoma

Tables 3 and **4** show the incidence of adverse events in the 158 patients in the anaplastic astrocytoma study for whom data are available. In the absence of a control group, it is not clear in many cases whether these events should be attributed to temozolomide or the patients' underlying conditions, but nausea, vomiting, fatigue, and hematologic effects appear to be clearly drug related. The most frequently occurring side effects were nausea, vomiting, headache, and fatigue. The adverse events were usually NCI Common Toxicity Criteria (CTC) Grade 1 or 2 (mild to moderate in severity) and were self-limiting, with nausea and vomiting readily controlled with antiemetics. The incidence of severe nausea and vomiting (CTC Grade 3 or 4) was 10% and 6%, respectively. Myelosuppression (thrombocytopenia and neutropenia) was the dose-limiting adverse event. It usually occurred within the first few cycles of therapy and was not cumulative.

Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range 21 to 40 days) and 28 days for neutrophils (range 1 to 44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir which may have delayed the start of the next cycle. Less than 10% of patients required hospitalization, blood transfusion, or discontinuation of therapy due to myelosuppression.

In clinical trial experience with 110 to 111 women and 169 to 174 men (depending on measurements), there were higher rates of Grade 4 neutropenia (ANC < 500 cells/μL) and thrombocytopenia (< 20,000 cells/μL) in women than men in the first cycle of therapy (12% versus 5% and 9% versus 3%, respectively).
In the entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients over age 70 experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. For patients less than or equal to age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and anemia have also been reported.

Table 3

Adverse Events in the Anaplastic Astrocytoma Trial in Adults(>5%)

	No. (%) of TEMODAR Patients (N=158)	
	All Events	Grade 3/4
Any Adverse Event	**153 (97)**	**79 (50)**
Body as a Whole		
Headache	65 (41)	10 (6)
Fatigue	54 (34)	7 (4)
Asthenia	20 (13)	9 (6)
Fever	21 (13)	3 (2)
Back pain	12 (8)	4 (3)
Cardiovascular		
Edema peripheral	17 (11)	1 (1)
Central and Peripheral Nervous System		
Convulsions	36 (23)	8 (5)
Hemiparesis	29 (18)	10 (6)
Dizziness	19 (12)	1 (1)
Coordination abnormal	17 (11)	2 (1)
Amnesia	16 (10)	6 (4)
Insomnia	16 (10)	0
Paresthesia	15 (9)	1 (1)
Somnolence	15 (9)	5 (3)
Paresis	13 (8)	4 (3)
Urinary incontinence	13 (8)	3 (2)
Ataxia	12 (8)	3 (2)
Dysphasia	11 (7)	1 (1)
Convulsions local	9 (6)	0
Gait abnormal	9 (6)	1 (1)
Confusion	8 (5)	0
Endocrine		
Adrenal hypercorticism	13 (8)	0
Gastrointestinal System		
Nausea	84 (53)	16 (10)
Vomiting	66 (42)	10 (6)
Constipation	52 (33)	1 (1)
Diarrhea	25 (16)	3 (2)
Abdominal pain	14 (9)	2 (1)
Anorexia	14 (9)	1 (1)
Metabolic		
Weight increase	8 (5)	0

Musculoskeletal System		
Myalgia	8 (5)	
Psychiatric Disorders		
Anxiety	11 (7)	1 (1)
Depression	10 (6)	0
Reproductive Disorders		
Breast pain, female	4 (6)	
Resistance Mechanism Disorders		
Infection viral	17 (11)	0
Respiratory System		
Upper respiratory tract infection	13 (8)	0
Pharyngitis	12 (8)	0
Sinusitis	10 (6)	0
Coughing	8 (5)	0
Skin and Appendages		
Rash	13 (8)	0
Pruritus	12 (8)	2 (1)
Urinary System		
Urinary tract infection	12 (8)	0
Micturition increased frequency	9 (6)	0
Vision		
Diplopia	8 (5)	0
Vision Abnormal*	8 (5)	

*Blurred vision, visual deficit, vision changes, vision troubles.

Table 4
Adverse Hematologic Effects (Grade 3 to 4) in the Anaplastic Astrocytoma Trial in Adults

	TEMODAR[a]
Hemoglobin	7/158 (4%)
Lymphopenia	83/152 (55%)
Neutrophils	20/142 (14%)
Platelets	29/156 (19%)
WBC	18/158 (11%)

[a]Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

In addition, the following spontaneous adverse experiences have been reported during the marketing surveillance of TEMODAR Capsules: allergic reactions, including rare cases of anaphylaxis. Rare cases of erythema multiforme have been reported which resolved after discontinuation of TEMODAR and, in some cases, recurred upon rechallenge. Rare cases of opportunistic infections including *Pneumocystis carinii* pneumonia (PCP) have also been reported. Prolonged pancytopenia, which may result in aplastic anemia, has been reported very rarely.

OVERDOSAGE

Doses of 500, 750, 1,000, and 1,250 mg/m ^{2} (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported with any dose but is expected to be more severe at higher doses. An overdose of 2,000 mg per day for 5 days was taken by one patient and the adverse events reported were pancytopenia, pyrexia, multi-organ failure, and death. There are reports of patients who have taken more than 5 days of treatment (up to 64

days) with adverse events reported including bone marrow suppression, which in some cases was severe and prolonged, and infections and resulted in death. In the event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

DOSAGE AND ADMINISTRATION

Dosage of TEMODAR Capsules must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and the neutrophil and platelet counts at the time of initiating the next cycle. For TEMODAR dosage calculations based on body surface area (BSA) see **Table 9**. For suggested capsule combinations on a daily dose see **Table 10**.

Patients with Newly Diagnosed High Grade Glioma:

Concomitant Phase

TEMODAR is administered orally at 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60Gy administered in 30 fractions) followed by maintenance TEMODAR for 6 cycles. Focal RT includes the tumor bed or resection site with a 2-3 cm margin. No dose reductions are recommended during the concomitant phase; however, dose interruptions or discontinuation may occur based on toxicity. The TEMODAR dose should be continued throughout the 42 day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10^9 /L platelet count ≥ 100 x 10^9/L common toxicity criteria (CTC) non-hematological toxicity ≤Grade 1 (except for alopecia, nausea, and vomiting). During treatment, a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in **Table 5.** PCP prophylaxis is required during the concomitant administration of TEMODAR and radiotherapy and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC grade ≤ 1).

Table 5 Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	TMZ Interruption[a]	TMZ Discontinuation
Absolute Neutrophil Count	≥0.5 and <1.5 x 10^9/L	<0.5 x 10^9/L
Platelet Count	≥10 and <100 x 10^9/L	<10 x 10^9/L
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ could be continued when all of the following conditions are met: absolute neutrophil count ≥1.5 x 10^9/L; platelet count ≥100 x 10^9/L; CTC non-hematological toxicity ≤Grade 1 (except for alopecia, nausea, vomiting).

TMZ = temozolomide; CTC = Common Toxicity Criteria.

Maintenance Phase Cycle 1:
Four weeks after completing the TEMODAR + RT phase, TEMODAR is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment.

Cycles 2-6:
At the start of Cycle 2, the dose is escalated to 200 mg/m^2, if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea, and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the platelet count is ≥ 100 x 10^9/L. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles.

Dose reduction or discontinuation during maintenance:
Dose reductions during the maintenance phase should be applied according to Tables **6** and **7**.
During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose of TEMODAR) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to Tables **6 and 7**.

Table 6 Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
–1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 7 Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level[a]	Discontinue TMZ
Absolute Neutrophil Count	<1.0 x 10^9/L	See footnote b
Platelet Count	<50 x 10^9/L	See footnote b
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

a: TMZ dose levels are listed in Table 6.

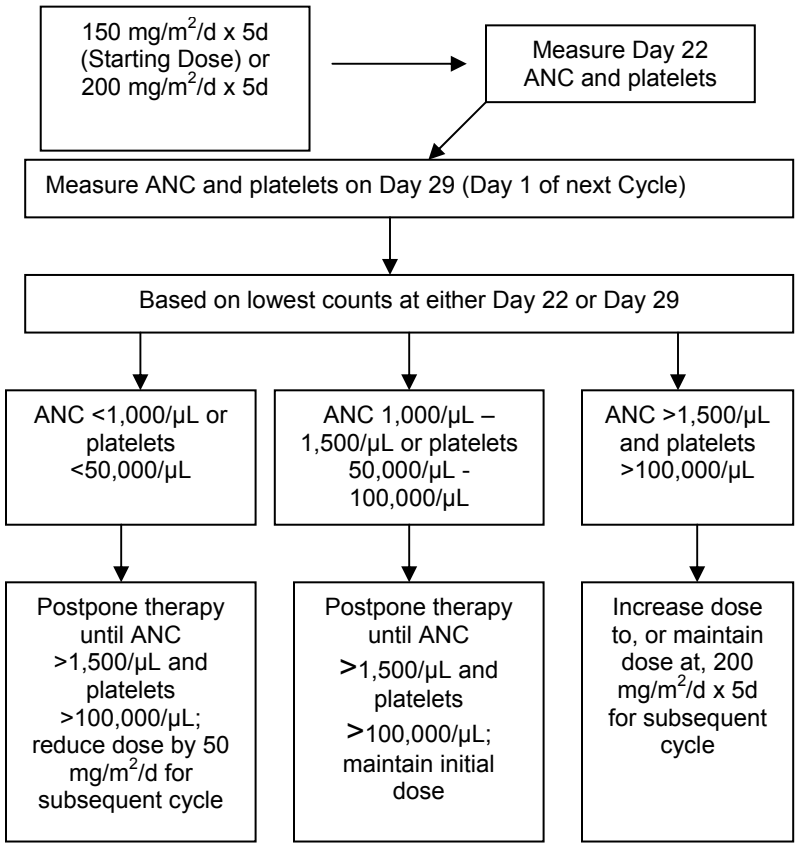
b: TMZ is to be discontinued if dose reduction to <100 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

TMZ = temozolomide; CTC = Common Toxicity Criteria.

Patients with Refractory Anaplastic Astrocytoma

For adults the initial dose is 150 mg/m^2 orally once daily for 5 consecutive days per 28-day treatment cycle. For adult patients, if both the nadir and day of dosing (Day 29, Day 1 of next cycle) ANC are $\geq$1.5 x 10^9/L (1,500/µL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are $\geq$100 x 10^9/L (100,000/µL), the TEMODAR dose may be increased to 200 mg/m^2/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. If the ANC falls to <1.0 x 10^9/L (1,000/µL) or the platelet count is <50 x 10^9/L (50,000/µL) during any cycle, the next cycle should be reduced by 50 mg/m^2, but not below 100 mg/m^2, the lowest recommended dose (see **Table 8**). TEMODAR therapy can be continued until disease progression. In the clinical trial, treatment could be continued for a maximum of 2 years; but the optimum duration of therapy is not known.

Table 8 Dosing Modification Table



480
481 **Table 9**
482 Daily Dose Calculations by Body Surface Area (BSA)
483

Total BSA (m^2)	75 mg/m^2 (mg daily)	150 mg/m^2 (mg daily)	200 mg/m^2 (mg daily)
1.0	75	150	200
1.1	82.5	165	220
1.2	90	180	240
1.3	97.5	195	260
1.4	105	210	280
1.5	112.5	225	300
1.6	120	240	320
1.7	127.5	255	340
1.8	135	270	360
1.9	142.5	285	380
2.0	150	300	400
2.1	157.5	315	420
2.2	165	330	440
2.3	172.5	345	460
2.4	180	360	480
2.5	187.5	375	500

484

Table 10

Suggested Capsule Combinations Based on Daily Dose in Adults

	Number of Daily Capsules by Strength (mg)			
Total Daily Dose (mg)	**250**	**100**	**20**	**5**
75	0	0	3	3
82.5	0	0	4	0
90	0	0	4	2
97.5	0	1	0	0
105	0	1	0	1
112.5	0	1	0	2
120	0	1	1	0
127.5	0	1	1	1
135	0	1	1	3
142.5	0	1	2	0
150	0	1	2	2
157.5	0	1	3	0
165	0	1	3	1
172.5	0	1	3	2
180	0	1	4	0
187.5	0	1	4	1
195	0	1	4	3
200	0	2	0	0
210	0	2	0	2
220	0	2	1	0
225	0	2	1	1
240	0	2	2	0

Table 10 *continued*

Suggested Capsule Combinations Based on Daily Dose in Adults				
	Number of Daily Capsules by Strength (mg)			
Total Daily Dose (mg)	**250**	**100**	**20**	**5**
255	1	0	0	1
260	1	0	0	2
270	1	0	1	0
280	1	0	1	2
285	1	0	1	3
300	0	3	0	0
315	0	3	0	3
320	0	3	1	0
330	1	0	4	0
340	0	3	2	0
345	0	3	2	1
360	0	3	3	0
375	1	1	1	1
380	1	1	1	2
400	0	4	0	0
420	0	4	1	0
440	0	4	2	0
460	1	2	0	2
480	1	2	1	2
500	2	0	0	0

In clinical trials, TEMODAR was administered under both fasting and non-fasting conditions; however, absorption is affected by food (see **CLINICAL PHARMACOLOGY**) and consistency of administration with respect to food is recommended. There are no dietary restrictions with TEMODAR. To reduce nausea and vomiting, TEMODAR should be taken on an empty stomach. Bedtime administration may be advised. Antiemetic therapy may be administered prior to and/or following administration of TEMODAR Capsules.

TEMODAR (temozolomide) Capsules should not be opened or chewed. They should be swallowed whole with a glass of water.

Handling and Disposal: TEMODAR causes the rapid appearance of malignant tumors in rats. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered[1-7]. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

TEMODAR (temozolomide) Capsules are supplied in amber glass bottles with child resistant polypropylene caps containing the following capsule strengths:

TEMODAR (temozolomide) Capsules 5 mg: 5 and 20 capsule bottles.

5 count - NDC 0085-1248-01 20 count - NDC 0085-1248-02

TEMODAR (temozolomide) Capsules 20 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1244-01 20 count - NDC 0085-1244-02
TEMODAR (temozolomide) Capsules 100 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1259-01 20 count - NDC 0085-1259-02
TEMODAR (temozolomide) Capsules 250 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1252-01 20 count - NDC 0085-1252-02

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
[See USP Controlled Room Temperature]

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4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australi*a. 1983;1:426-428.
5. Jones RB, et al. Safe Handling Of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA - *A Cancer Journal for Clinician*s. 1983;(Sept/Oct):258-263.
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